# POSSIBLE UPREGULATION OF MACROPHAGE RESPONSIVENESS TO WEAR DEBRIS

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## INTRODUCTION

The macrophage response to wear debris is a key event in an inflammatory cascade leading to periprosthetic bone loss around total hip replacements (THR)[1,2] Previous investigations suggest that patients with THR may have more sensitive macrophages[3], which in turn respond more aggressively to wear debris.

To test this hypothesis, we have compared the responsiveness of peripheral blood monocytes from canines with and without THR, to UHMWPE and other particulate wear debris.

## MATERIALS AND METHODS

Peripheral blood was drawn from 20 adult male canines (30-35 kg). 15/20 had uncemented THR 24 weeks prior to blood draw and 5/20 did not have any joint replacements. Monocytes were harvested over discontinous Percoll gradients, overnight adherence depleted of contaminating cells and cultured in serum free media (M-SFM, GIBCO, NY)[4]. Wear debris cultured with macrophages were either: TiAlV (mean 3.1 μm), CoCr-alloy (mean 0.8 μm), fabricated UHMWPE (mean 2.3 μm) or a Mix of 90% by number of UHMWPE, 5% TiAlV and 5% CoCr. Dosages of debris were based on cell surface area and were 0.2x, 1x and 5x the estimated cultured cell surface area (CSA)[4]. Cells cultured without debris represented non-stimulated (NS) cells and phorbol myristate acetate (PMA, 1 μg/well) was added as a positive control. After a 72 h co-culture, supernatants were harvested and stored frozen until assayed for prostaglandin $E_2$ ($PGE_2$) and interleukin-1 (IL-1)[3]. Data was analyzed using post hoc T-tests.

## RESULTS

*Control Canine Macrophages:* Non-stimulated macrophages from control animals released basal levels of $PGE_2$ and IL-1. Culturing macrophages with wear debris resulted in a surface area dependent increase in mediator release. TiAlV particles elicited a 3-fold and 10-fold increase in $PGE_2$ compared to NS cells at the 1x and 5x CSA, respectively (Fig. 1). PE particles were dramatically more stimulatory and elicited a 33-fold, 55-fold and an 18-fold increase in $PGE_2$ release at the three dosages studied (Fig. 1).

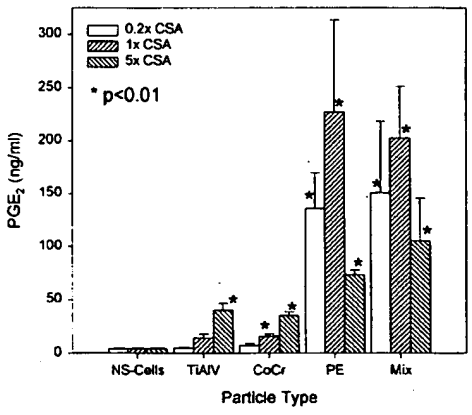


**Figure 1:** $PGE_2$ release by macrophages cultured with wear debris (mean±SE)

*THR Canine Macrophages:* Macrophage from canines with THR were consistently more stimulatory to wear debris than macrophages from control canines (Fig. 2). While this trend was observed at all particle doses, it was maximal at the 0.2x CSA. $PGE_2$ release by NS cells from THR recipients were elevated 40% compared to control canines. TiAlV and CoCr debris elicited 60% and 145% higher levels of $PGE_2$ compared to similarly stimulated cells from control canines. In spite of the dramatic stimulatory effect of PE particles in control canines, PE and Mix debris further increased macrophage mediator release by 88% ($p<0.1$) & 44% respectively.

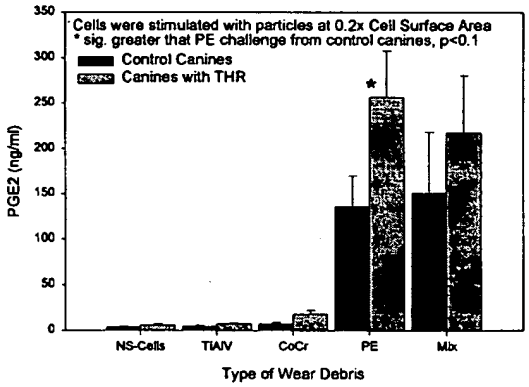


**Figure 2:** Upregulation of $PGE_2$ release in canines with THR (mean±SE).

## DISCUSSION

Control canine macrophages clearly demonstrate the intense stimulatory nature of wear debris, particularly PE and the Mix debris. Performing a THR in the canine appears to pre-sensitize the macrophages, such that they respond more aggressively to subsequent in-vitro culture with wear debris. If a similar pre-sensitization occurs in the clinical population, the macrophage response to debris may be more severe clinically than previously estimated based on in-vitro studies in control subjects[4]. If the extent of presensitization varies among patients, it may explain why only some THR patients develop osteolysis while others have long, useful lifespans.

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**References**

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